REMARKS/ARGUMENTS

Claims 1, 7, 9 and 11 have been amended and new claim 27 added to more specifically claim the Applicant's invention. These amendments were made without prejudice to subject matter than may be claimed in subsequent applications related to the present case. No new matter was included in the amended or new claims.

The Applicants' representative would like to thank Examiner Webman for his courtesy during a brief informal telephonic interview conducted February 13, 2006. During that telephonic interview the Examiner and Applicants' representative, Mr. Cullman, discussed the outstanding office action, claim scope and cited prior art. Although no agreements were reached as to allowability, the claim amendments and arguments present herein reflect the substance of the February 13, 2006 informal interview.

Claim Rejections under 35 U.S.C. §103 (a)

Claims 1, 2, 5-7, 21 and 25 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Hossainy et al. in view of Dasseux. Briefly, the Examiner states that Hossainy teaches coated stents that reduce the incidence of restenosis through the delivery of therapeutic agents contained in the coating, specifically Hossainy et al. teaches rapamycin analogues. Dasseux teaches drug coated stents to reduce restenosis. Further, the Examiner asserts that Dasseux teaches using rosiglitazone (a PPARγ agonist). Thus the Examiner asserts that it would have obvious for one skilled in the art to combine Hossainy et al. with Dasseux to arrive at the claimed invention. The Applicants respectfully disagree.

The Applicants have cancelled claim 21, 22 and 25 that specifically claim using PPARγ agonists in combination with rapamycin analogues. Furthermore, the Applicants have amended claims 1, 7, 9 and 11 to exclude anti-restenotic therapeutic agents other than PPARγ agonists from the controlled release, *in situ*, from therapeutic delivery devices as presently claimed.

Therefore, because claims in the present case are now limited to medical devices for the *in situ* controlled release of a single class of therapeutic agents, specifically PPARγ agonists, the Examiner's *prima facie* case of obviousness vis-à-vis open-ended claims, or claims directed to the co-delivery (via an implantable medical device) of multiple therapeutic agents are now moot.

Moreover, the Applicants respectfully assert that Hossainy et al and Dasseux cannot be combined to establish a *prima facie* case of obviousness against any pending claims when considered in light of the present claim amendments.

To accommodate the Examiner and in the interest of prosecution efficiency, a brief non-limiting synopsis of the present invention follows.

Applicants' present invention is now directed to *in situ* peroxisome proliferator-activated receptor gamma (PPARγ) agonist controlled-release delivery using therapeutic agent eluting medical devices, wherein the devices include stents, catheters, microparticles, probes and vascular stents. The present application states, in part,

> "[0023] [t]he present invention includes novel compositions and methods for delivering peroxisome proliferator-activated receptor gamma (PPARγ) agonists directly to tissues susceptible to restenosis. Specifically, the present invention is directed at implantable medical devices that provide for the *in situ*, site-specific controlled release of ligands that bind to and activate PPARγ receptors. Once activated, PPARγ receptors inhibit vascular smooth muscle cell (VSMC) proliferation.
>
> [0031] In one embodiment of the present invention vascular stents are implanted into coronary arteries immediately following angioplasty. However, one significant problem associated with stent implantation, specifically vascular stent deployment, is restenosis. Restenosis is a process whereby a previously opened lumen is re-occluded by VSMC proliferation. Therefore, it is an object of the present invention to provide stents that suppress or eliminate VSMC migration and proliferation and thereby reduce, and/or prevent restenosis.
>
> [0032] In one embodiment of the present invention metallic vascular stents are coated with one or more anti-restenotic compound, specifically PPARγ agonists, more specifically the PPARγ agonists are thiazolidinediones."

Without reciting the entire text, Example 6-8 are included herein. This text may be found from paragraphs [0070] – [0088] in Applicants' present invention. Example 6 shows the inhibition of human coronary artery smooth muscle cells by ciglitazone, Example 7 shows the

inhibition of human coronary artery endothelial cells by ciglitazone, and Example 8 shows the inhibition of human coronary artery smooth muscle cells by rosiglitazone.

The Applicant has further defined his invention in the present application by claiming only a single aspect of what is disclosed in the application. Specifically, the Applicant has amended their claims to limit the present application to the controlled release *in situ* delivery of a single therapeutic agent class, specifically, PPARγ agonists.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met according to the Manual of Patent Examining Procedure, §706.02(j). These three are repeated as follows. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness regarding presently pending, and as amended, claims 1, 2, 5-7, 9 and 11.

In regard to the first criterion of obviousness, there is no suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine the reference teachings. Regarding the Hossainy et al. reference, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Hossainy et al. teach a process for coating surgical devices generally. (Column 1, lines 7-10). The Examiner specifically cites this reference because rapamycin is disclosed. However, the present claims have been amended to exclude therapeutic agents other than PPARγ agonists. Hossainy et al. do not disclose incorporating PPARγ agonists into the coating.

It is important to note that PPARγ agonists, including rosiglitazone, were known at least prior to the Hossainy et al. filing date (see for example the filing date of USPN 5,859,037 filed in November 1997). Therefore, it is appropriate to conclude that Hossainy et al. had the opportunity to include PPARγ agonists in its disclosure, and did not do so. As a matter of fact, even though PPARγ agonists was clearly known prior to the filing date of the Hossainy et al. reference, Hossainy et al. is silent as to the entire class of PPARγ agonists including

thiazolidinediones, to which rosiglitazone belongs. The Examiner originally cited Hossainy et al as analogous prior art because Hossainy et al suggested including rapamycin in a stent coating. The rapamycin limitation has been eliminated from the present claims and thus the Applicants respectfully assert that Hossainy et al. is no longer analogous prior art and there is no basis for combining Hossainy et al. with Dasseux.

Regarding the Dasseux reference, the Examiner states that Dasseux teaches drug coated stents to reduce the risk of restenosis and that rosiglitazone is specified in a list of drugs that can be used in combination with the novel compounds disclosed in Dasseux. While this is true generally speaking, Dasseux does not specifically teach a stent having a controlled release coating consisting essentially of at least one polymer and at least one PPARγ agonist as presently claimed, nor does Dasseux fairly suggest such an embodiment as claimed. The PPARγ agonist rosiglitazone is mentioned only in passing and not as a compound suitable for incorporation into a medical device coating. Rather, the Dasseux reference states, "[t]he present invention provides *novel compounds* having the general formula I." (Emphasis added). (Column 21, lines 53-55). None of the "novel compounds" based on formula 1 at disclosed as being thiazolidinediones (the class to which rosiglitazone, for example, belongs belong) or other forms of PPARγ agonist. Rather, the reference discloses:

> "[i]n certain embodiments of the invention, a compound of formula I or a pharmaceutically acceptable salt thereof is administered in combination with *another therapeutic agent.* The *other therapeutic agent* provides additive or synergistic value relative to the administration of a compound of formula I alone. The therapeutic agent can be...*a* PPARγ agonist." (Column 24, lines 34-40). (Emphasis added).

Thus, it is apparent that the "novel compounds" disclosed in Dasseux are not themselves PPARγ agonists or Dasseux would not have referred to PPARγ agonists as "another therapeutic agent..." as discussed *supra.*

Additonally, Dauseux lacks an enabling disclosure for a controlled release rosiglitazone coated stent. Further, the Dasseux reference actually teaches away from implantable medical devices that provide for the *in situ*, site-specific controlled release of ligands that bind to and activate PPARγ receptors as presently claimed. Dasseux teaches away by expressly stating that

"the compound of formula I or a pharmaceutically acceptable salt thereof is administered in combination with another therapeutic agent. The therapeutic agent can be...a PPARγ agonist." Therefore, the Dasseux reference discloses that the only way a PPARγ agonist may be used in accordance with their alleged invention is to use it with a "novel compound" of the Dasseux disclosure. The present invention no longer claims using a PPARγ agonist *in combination with another therapeutic agent.* The Applicants respectably submit that Dasseux teaches away from the use of PPARγ agonist the sole class of therapeutic agent used to treat restenosis and does not teach the controlled release of a PPARγ agonist from a medical device coating and is therefore *not analogous* to either the present invention or Hossainy et al. Therefore, Dasseux and Hossainy et al cannot be combined to establish a *prima facie* case of obviousness vis-à-vis the present claims.

In regard to the second criterion of obviousness, there is no reasonable expectation that the combination would be successful. Undoubtedly, even if one were to combine the references discussed herein, one would have to conduct undue experimentation to achieve Applicants' present invention. Whereas Applicants' present invention teaches one skilled in the art, among other things, how to provide a medical device with a controlled release coating using a drug/polymer system having a PPARγ agonist as presently claimed. None of the above-noted references, when considered alone or in combination, teach and/or enable the skilled artisan to make the presently claimed invention in a manner sufficient to provide a reasonable probability of success without undue experimentation.

In regard to the third criterion of obviousness, the prior art references do not teach or suggest all the claim limitations. The above-noted references, taken either alone or together, do not teach or suggest at least a medical device having a site-specific delivery device for the biocompatible polymer-based, controlled release of at least one peroxisome proliferator-activated receptor gamma (PPARγ) agonist alone (as presently claimed).

Therefore the Applicants respectfully assert, that the cited references, whether taken alone, or in combination, do not establish a *prima facie* case of obviousness against the claims, as amended, and the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection of record and allow presently pending claims 1, 2, 5-7, 9, 11 and 27 to pass to issue.

Conclusion

For the foregoing reasons, Applicant believes all the pending claims are in condition for allowance and should be passed to issue. The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. 1.17, or credit any overpayment, to Deposit Account No. 01-2525. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at telephone (707) 543-5021.

Respectfully submitted,

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